Predictors of adverse outcome in adolescents and adults with isolated left ventricular noncompaction

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Abstract: Isolated left ventricular noncompaction is a rare form of primary cardiomyopathy. Although increasingly diagnosed, data on the outcomes are limited. To define the predictors of adverse outcomes, we performed a retrospective analysis of a prospectively defined cohort of consecutive patients (age >14 years) diagnosed with left ventricular noncompaction at a single center. The baseline characteristics included presentation with a cardiovascular complication (i.e., decompensated heart failure, systemic embolic event, or sustained ventricular arrhythmia). The primary end point was survival free from cardiovascular death or transplantation. The predictors of survival were evaluated using the Kaplan-Meier method and Cox proportional hazards analysis. A total of 115 patients were included, 77% of whom were symptomatic at diagnosis. Compared to the asymptomatic patients, the symptomatic patients were significantly older and had larger left ventricular cavities and worse left ventricular ejection fraction. Of the 115 patients, 49 (43%) presented with a cardiovascular complication. During a median follow-up of 2.7 years (range 0.1 to 19.4), none of the asymptomatic patients died or underwent transplantation compared to 31% (27 of 88) of the symptomatic patients (p = 0.001). The major determinants of cardiovascular death or transplantation were presentation with a cardiovascular complication (hazard ratio 20.6, 95% confidence interval 4.9 to 87.5, p <0.0001) or New York Heart Association class III or greater (hazard ratio 8.8, 95% confidence interval 3.2 to 24.0, p <0.0001). Left ventricular dilation and systolic dysfunction were less strong predictors. In conclusion, in patients with left ventricular noncompaction, New York Heart Association class III or greater and cardiovascular complications at presentation are strong predictors for adverse outcome.

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Predictors of Adverse Outcome in Adolescents and Adults with Isolated Left Ventricular Non-compaction

Running title: Outcome in patients with LVNC

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Abstract

Isolated left ventricular non-compaction (LVNC) is a rare form of primary cardiomyopathy. While increasingly diagnosed, data on outcomes are limited. To define predictors of adverse outcomes, we performed a retrospective analysis of a prospectively defined cohort of consecutive patients (age >14 years) diagnosed with LVNC at a single center. Baseline characteristics included presentation with a cardiovascular complication (decompensated heart failure, systemic embolic event or sustained ventricular arrhythmia). The primary endpoint was survival free from cardiovascular death or transplantation. Predictors of survival were evaluated using the Kaplan Meier method and a Cox Proportional Hazards analysis. A total of 115 patients were included, 77% of whom were symptomatic at diagnosis. Compared to asymptomatic patients, symptomatic patients were significantly older, had larger left ventricular cavities and worse left-ventricular ejection fraction. Forty-nine patients (43%) presented with a cardiovascular complication. During a median follow-up of 2.7 years (range: 0.1 – 19.4), none of the asymptomatic patients died or underwent transplantation compared to 31% (27/88) of the symptomatic patients ($p = 0.001$). The major determinants of cardiovascular death or transplantation were presentation with a cardiovascular complication (HR 20.6, 95% CI 4.9-87.5, $p<0.0001$) or NYHA class ≥3 (HR 8.8, 95% CI 3.2-24.0, $p<0.0001$). Left ventricular dilatation and systolic dysfunction were less strong predictors. In conclusion, in patients with LVNC, NYHA class ≥ 3 and cardiovascular complications at presentation are strong predictors for adverse outcome.

Key words: Isolated left ventricular non-compaction, outcome, cardiomyopathy

Isolated left ventricular non-compaction (LVNC) is a rare cardiomyopathy with considerable genetic heterogeneity.[1,2] Despite its increasing recognition and diagnosis, the clinical outcome of this rare entity is not well defined.[3-10 11-13]

The aim of this study was to examine clinical outcome in a relatively large, prospectively defined cohort of patients with LVNC and to identify risk factors for adverse cardiovascular events.

Methods

Diagnostic criteria as previously described by our group were used.[14] In the absence of other congenital or acquired structural heart disease or neuromuscular disorders, these criteria include the presence of a typical two-layered structure of a significantly thickened myocardium. The thickened two-layered myocardium consisted of a thin, compacted outer (epicardial) layer and a much thicker, non-compacted inner (endocardial) layer with deep intertrabecular recesses filled with blood from the left ventricular cavity. A ratio of the non-compacted to compacted layer of > 2, obtained in the parasternal short axis view, had to be present at end-systole. All diagnoses were established by echocardiography and required independent agreement by two experienced echocardiographers (RJ and EO). These criteria were previously validated against dilated cardiomyopathy, hypertensive heart disease and valvar heart disease and showed good sensitivity and specificity.[15] To define the extent of involvement, the left ventricle was divided into 9 segments as previously described.[5] Left ventricular dimensions and function at the time of diagnosis and in follow-up were assessed according to established guidelines for two-dimensional echocardiography.[16] Left ventricular dimensions were normalized for body surface area.

Left ventricular non-compaction was diagnosed in 152 consecutive patients over the age of 14 years at a single tertiary referral centre, University Hospital, Zurich (0.15% of all echocardiograms) between 1984 and 2006. Twenty patients were excluded for associated congenital heart disease. This left 132 patients with LVNC in the study cohort. The lower age limit of 14 years was chosen to allow enrollment of adolescents identified by family screening, but to avoid enrollment of neonatal LVNC or LVNC with onset of symptoms in early childhood, a disease entity which is often accompanied by syndromic association and may have a different outcome than LVNC diagnosed in adulthood.[4,6,8]

Clinical characteristics collected at initial presentation were the presence and nature of cardiac symptoms, functional class (New York Heart Association classification) and the occurrence of cardiovascular complications at the time of initial assessment or prior to presentation. The latter comprised decompensated heart failure requiring hospital admission, systemic embolic events, sustained ventricular arrhythmias and/or presentation with survived sudden cardiac death.

Figure 1 depicts the number of newly diagnosed patients with LVNC at our centre during the study period. The increased number of asymptomatic patients after the year 2000 reflects our policy of routine family screening.

Of the 132 patients within the study cohort 115 (87%) had at least one year of follow-up or died or underwent heart transplantation within the first 12 months after diagnosis. These 115 patients were included in the survival analysis. Follow-up information was collected by retrospective chart review. Initial presentation and outcome of the first 34 patients of the cohort has been reported previously.[5]

The primary endpoint included cardiovascular death or heart transplantation. Other major adverse events were recorded and included systemic embolism, sustained ventricular arrhythmias and admission for heart failure. Cardiovascular death was

defined as death directly related to progressive heart failure, sudden death (death within one hour of onset of symptoms or acute deterioration of a symptomatic patient with previously stable symptoms), death related to cardio-embolic stroke, death caused by pulmonary embolism or death ensuing in the immediate sequence of a cardiovascular intervention or operation.

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Descriptive data is presented as medians (range), means (± standard deviations) and proportions as appropriate. Comparison between survivors and non-survivors and the groups of patients presenting with and without symptoms was performed using Student's t-test, Mann Whitney or Chi square tests. Kaplan Meier curves were used to depict difference between patients with and without: a) symptoms at presentation, b) cardiovascular complications at presentation, c) NYHA class ≥3, d) left ventricular enddiastolic diameter indexed to body surface area > 3.7 cm/m^2 and left ventricular ejection fraction (LVEF) <35%. Predictors of survival free from cardiovascular death or heart transplantation were determined using a Cox proportional hazards model. A p-value <0.05 (two-sided) was considered to be significant.

Results

Clinical, echocardiographic and electrocardiographic baseline characteristics of the entire study cohort, survivors and patients with cardiovascular death/transplantation are summarized in ***Table 1***. At the time of diagnosis, 66 symptomatic patients (50%) were on medical treatment. Most common medications were angiotensin converting enzyme inhibitors or angiotensin receptor antagonists (36%), beta blockers (38%) and

diuretics (26%). Forty-eight patients (36%) were on oral anticoagulation and 9 (7%) on low dose Aspirin.

Ninety-five patients (72%) were symptomatic at the time of diagnosis. The most common symptoms reported by the patients were dyspnea (80%), syncope (16%) and palpitations (22%). A large proportion of symptomatic patients presented with a cardiovascular complication, including 3 survivors of a sudden cardiac death (***Table 1***). Three patients had a history of transient ischemic attack or stroke (1 month, 2 years and 10 years prior to the diagnosis of LVNC). All were known to have a cardiomyopathy at the time of the embolic event. Some patients presenting with symptoms had been previously labeled as 'dilated cardiomyopathy' (n = 23, 24%). In those cases the correct diagnosis of LVNC was delayed by 5.2 years (range: 0.2-17.3). Five patients (ages 40, 57, 64, 70 and 72 years) were found to have additional coronary artery disease during initial assessment.

The most common reason for assessment of asymptomatic patients (n = 37) was family screening (49%); a total of 30 patients (23%) in our cohort had one or more family members affected by LVNC. Other reasons for assessment of asymptomatic patients were non-cardiac chest pain, heart murmurs or ECG-abnormalities. Baseline characteristics of patients presenting with and without symptoms are compared in ***Table 2***. At the time of diagnosis 5 asymptomatic patients (14%) had an LVEF below 45% and one patient (3%) below 35%.

Serial follow-up data was available for 27 (73%) asymptomatic and for 88 (93%) symptomatic patients. The median follow-up time until last clinic visit or cardiovascular death/heart transplantation was 2.7 (range: 0.1 – 19.4) years and was not significantly different between survivors and non-survivors [2.7 years (range 1.0-15.8) versus 1.9 years (range 0.1-19.4), p = 0.14]. ***Table 3*** presents the adverse cardiovascular events in the 115 patients at risk. None of the asymptomatic patients experienced any adverse

cardiovascular events during follow-up, irrespective of whether they had been diagnosed incidentally or by family screening. One asymptomatic patient (4%) had progressive left ventricular dilatation with increase of left ventricular enddiastolic diameter from 5.2 cm at presentation to 7.2 cm with corresponding decrease in LVEF from 50% to 35% (follow-up period of 7.9 years). This patient underwent implantation of an implantable cardioverter defibrillator (AICD) for primary prevention of sudden cardiac death after induction of polymorphic ventricular tachycardia on electrophysiological testing (one year after diagnosis). At the time of his last clinical follow up, he remained asymptomatic, continued to have a good exercise tolerance and had not experienced any AICD discharges. All other patients without symptoms at diagnosis had stable left ventricular dimensions and systolic function during follow up.

Thirty two patients (28%) experienced a total of 52 adverse cardiovascular events. Twenty-one patients (18%) died from cardiovascular cause and 6 (5%) underwent orthotopic heart transplantation. Sudden cardiac death (48%) was the most common cause of death followed by death due to progressive heart failure (38%). One patient (5%) died from pulmonary embolism and two patients (10%) died due to a complication after cardiac device implantation. Of patients experiencing cardiovascular complications, 2 had concomitant coronary artery disease on initial assessment. One of these patients died from progressive heart failure and one from postoperative sepsis after AICD implantation.

Out of five patients (4%) with systemic embolic events during follow-up, one had atrial fibrillation at the time of the event and only one was on oral anticoagulation after successful electrical cardioversion 7 months earlier. The INR was in the therapeutic range at the time of the event. There were no significant differences in age at diagnosis, left ventricular dimensions and left ventricular function between patients with and without systemic embolic events.

Survival free from cardiovascular death or heart transplantation was 86%, 75% and 36% at 1, 5 and 10 years, respectively. Univariate determinants of survival free from cardiovascular death or transplantation are given in ***Table 4***; ***Figure 2*** shows the Kaplan-Meier survival curves for the probability of survival free from cardiovascular death or transplantation according to clinical and echocardiographic characteristics.

Presentation in NYHA functional class ≥ 3 or presentation with a cardiovascular complication (defined as sustained ventricular arrhythmia, systemic embolization or admission with heart failure) were the strongest predictors of the primary endpoint, while echocardiographic (left ventricular dilatation and systolic dysfunction) and electrocardiographic parameters were less strong predictors. There was strong colinearity between all significant univariate predictors, precluding multivariate analysis.

Discussion

Although awareness of LVNC has substantially increased and several small series have been published during the last years, overall clinical event rates and predictors for poor outcome remain ill-defined.[4-12] In this prospectively defined cohort, we were able to define the clinical and echocardiographic characteristics of a relatively large population of patients with LVNC and to define distinct predictors of cardiovascular death or heart transplantation. Symptomatic patients had a high mortality and were at high risk for major adverse cardiovascular events. By univariate analysis, the strongest predictors for cardiovascular death or heart transplantation were presentation with a cardiovascular complication and functional class 3 or more. Adverse left ventricular remodeling with left ventricular dilatation and depressed left ventricular ejection fraction were less predictive.

In agreement with previous reports patients without symptoms at initial presentation had a more favorable short- and mid-term outcome.[10-12] None of them

developed symptoms or had cardiovascular complications albeit five patients had impaired left ventricular systolic function at presentation and one had progressive left ventricular dilatation and systolic dysfunction during follow-up. However, follow-up in these patients was limited and not long enough to be reassured about their long-term prognosis. Some of these individuals will likely develop progressive left ventricular dysfunction and are at risk for the development of symptoms and complications later in life.

It is concerning that in this series more than half of symptomatic patients presented with a clinical cardiovascular complication, including 9 patients (9%) with sustained ventricular arrhythmias and 3 patients (3%) with systemic embolization. By extrapolation from other forms of cardiomyopathy we speculate that at least some of these serious complications might have been preventable by early diagnosis, timely institution of evidence based heart failure medication and appropriate device therapy.[17]

Adverse outcomes including mortality and morbidity of patients with LVNC vary significantly among different reports and might have been overestimated in earlier studies because of inclusion of primarily symptomatic patients referred to tertiary referral centers.[4-6,9,12] It is of interest, that event rates were lower in recently published cohorts than in the previous reports.[9,13] In one, recently published series, no deaths occurred in patients with normal left ventricular ejection fraction and all patients who died were older than 70 years of age.[13] These more favorable outcomes in more recently published series are likely explained by the inclusion of asymptomatic patients and are consistent with findings from our present cohort. Application of evidence-based heart failure therapy may be another contributor to the more favorable outcome in more recent series. Interestingly, in one series, outcome of patients with LVNC was found to be comparable to outcomes in matched patients with dilated cardiomyopathy; this observation suggests

that the resultant LV dysfunction, rather than the phenotype or non-compacted myocardium itself, is the primary source of morbidity and mortality [13].

It would be obvious that sarcomere gene mutations may predict the clinical phenotype. However, in a recent study comparing sarcomere-mutation positive and mutation-negative LVNC probands, no significant differences in terms of the clinical phenotype was found. Thus, research is needed to clarify the relationship between the type of mutation, genetic modifiers, and the clinical phenotype. [18]

Our findings underscore the need for regular follow-up of patients with this rare cardiomyopathy, in particular close follow-up of symptomatic patients. Given the high incidence of complications at presentation, one of our primary goals must be to identify patients at risk before complications occur. Offering family screening to relatives of patients with an established diagnosis is therefore important. This may allow early identification of asymptomatic patients at risk for complications in the future. Timely institution of evidence based heart failure treatment in asymptomatic patients with worsening left ventricular systolic function may prevent the occurrence of complications.

There remain however some unresolved problems. In the absence of definitive diagnostic criteria, such as genetic testing, the diagnosis of LVNC is established by cardiac imaging, most commonly by echocardiography. There are, however, no generally accepted criteria on cardiac imaging for establishing the diagnosis of LVNC. The criteria proposed by our group and most frequently used by researchers are based on the presence of a thickened, two-layered myocardium with a ratio between non-compacted and compacted myocardium in affected segments of at least 2:1 measured during systole in the parasternal short axis view.[14] It has been reported that these criteria may be too sensitive, particularly in black patients.[19] This leaves us with the dilemma of potentially overcalling the diagnosis in otherwise healthy individuals with all its

implications and even potential implications on insurability. On the other hand, our criteria seem to identify a high risk group of symptomatic patients.

Although this is one of the largest populations of patients with LNVC, this study is still limited by the relatively small number of patients, by the referral bias, by the limited follow-up time and by the absence of universally accepted diagnostic criteria for LVNC. We have tried to overcome some of the operator dependent factors, which may affect interpretation of images by independent review of the images by two experienced echocardiographers (RJ and EO). Differences in interpretation were adjudicated by reviewers by joint interpretation. Systematic family screening of all affected patients was not available which may underestimate the number of asymptomatic individuals. In addition, our study population was recruited from a tertiary referral center and may represent a highly selected group. The true prevalence of LNVC in the general population and thus the general outcome of asymptomatic patients with LVNC are still not known and need to be further elucidated. Because of strong colinearity between significant univariate predictors, we were unable to perform a multivariate survival analysis.

1. Xing Y, Ichida F, Matsuoka T, Isobe T, Ikemoto Y, Higaki T, Tsuji T, Haneda N, Kuwabara A, Chen R, Futatani T, Tsubata S, Watanabe S, Watanabe K, Hirono K, Uese K, Miyawaki T, Bowles KR, Bowles NE, Towbin JA. Genetic analysis in patients with left ventricular noncompaction and evidence for genetic heterogeneity. *Mol Genet Metab* 2006;88:71-77.

2. Zaragoza MV, Arbustini E, Narula J. Noncompaction of the left ventricle: primary cardiomyopathy with an elusive genetic etiology. *Curr Opin Pediatr* 2007;19:619-627.

3. Jenni R, Goebel N, Tartini R, Schneider J, Arbenz U, Oelz O. Persisting myocardial sinusoids of both ventricles as an isolated anomaly: echocardiographic, angiographic, and pathologic anatomical findings. *Cardiovasc Intervent Radiol* 1986;9:127-131.

4. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. *Circulation* 1990;82:507-513.

5. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol* 2000;36:493-500.

6. Ichida F, Hamamichi Y, Miyawaki T, Ono Y, Kamiya T, Akagi T, Hamada H, Hirose O, Isobe T, Yamada K, Kurotobi S, Mito H, Miyake T, Murakami Y, Nishi T, Shinohara M, Seguchi M, Tashiro S, Tomimatsu H. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. *J Am Coll Cardiol* 1999;34:233-240.

7. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, Craigen WJ, Wu J, El Said H, Bezold LI, Clunie S, Fernbach S, Bowles NE, Towbin JA. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. *Circulation* 2003;108:2672-2678.

8. Wald R, Veldtman G, Golding F, Kirsh J, McCrindle B, Benson L. Determinants of outcome in isolated ventricular noncompaction in childhood. *Am J Cardiol* 2004;94:1581-1584.

9. Murphy RT, Thaman R, Blanes JG, Ward D, Sevdalis E, Papra E, Kiotsekoglou A, Tome MT, Pellerin D, McKenna WJ, Elliott PM. Natural history and familial characteristics of isolated left ventricular non-compaction. *Eur Heart J* 2005;26:187-192.

10. Lofiego C, Biagini E, Pasquale F, Ferlito M, Rocchi G, Perugini E, Bacchi-Reggiani L, Boriani G, Leone O, Caliskan K, ten Cate FJ, Picchio FM, Branzi A, Rapezzi C. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. *Heart* 2007;93:65-71.

11. Habib G, Charron P, Eicher JC, Giorgi R, Donal E, Laperche T, Boulmier D, Pascal C, Logeart D, Jondeau G, Cohen-Solal A. Isolated left ventricular non-compaction in adults: clinical and echocardiographic features in 105 patients. Results from a French registry. *Eur J Heart Fail* 2011;13:177-185.

12. Aras D, Tufekcioglu O, Ergun K, Ozeke O, Yildiz A, Topaloglu S, Deveci B, Sahin O, Kisacik HL, Korkmaz S. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. *J Card Fail* 2006;12:726-733.

13. Stanton C, Bruce C, Connolly H, Brady P, Syed I, Hodge D, Asirvatham S, Friedman P. Isolated left ventricular noncompaction syndrome. *Am J Cardiol* 2009;104:1135-1138.

14. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart* 2001;86:666-671.

15. Frischknecht BS, Attenhofer Jost CH, Oechslin EN, Seifert B, Hoigne P, Roos M, Jenni R. Validation of noncompaction criteria in dilated cardiomyopathy, and valvular and hypertensive heart disease. *J Am Soc Echocardiogr* 2005;18:865-872.

16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.

17. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009;53:e1-e90.

18. Probst S, Oechslin E, Schuler P, Greutmann M, Boye P, Knirsch W, Berger F, Thierfelder L, Jenni R, Klaassen S. Sarcomere Gene Mutations in Isolated Left Ventricular Noncompaction Cardiomyopathy Do Not Predict Clinical Phenotype. *Circ Cardiovasc Genet* 2011.

19. Kohli SK, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, Sharma S, Elliott PM. Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? *Eur Heart J* 2008;29:89-95.

Figure legends

Figure 1: Number of patients newly diagnosed with isolated left ventricular non-compaction at our centre 1984 and 2006

Figure 2: Probability of survival free from cardiovascular death or transplantation (Kaplan Meier curves).
Panel A: Overall survival. Panel B: Survival stratified for presentation with symptoms; Panel C: Survival stratified for presentation with a clinical complication (decompensated heart failure, sustained ventricular arrhythmia, systemic embolic event); Panel D: Survival stratified for NYHA class $\geq$ 3 at presentation; Panel E: Survival stratified for severe left ventricular dilatation at presentation; Panel F: Survival stratified for severe left ventricular systolic dysfunction at presentation.